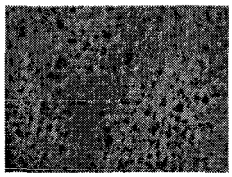
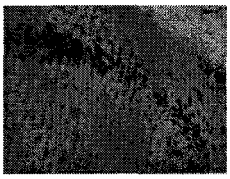
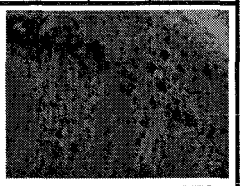
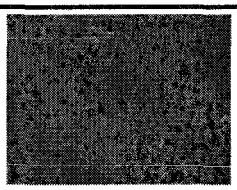
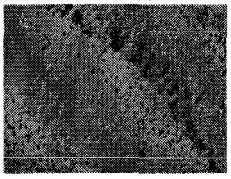
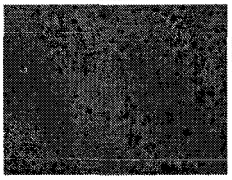
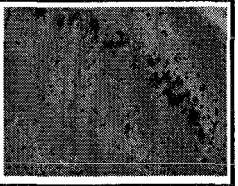
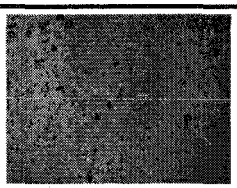
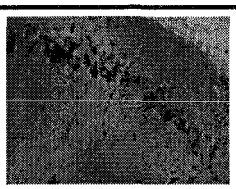
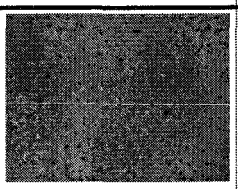
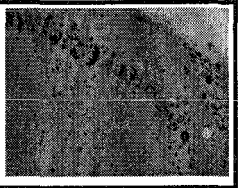
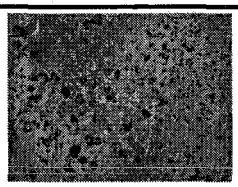
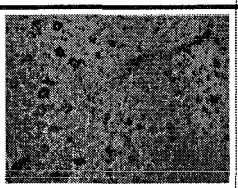
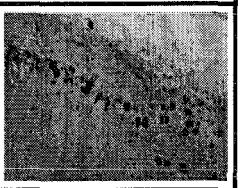
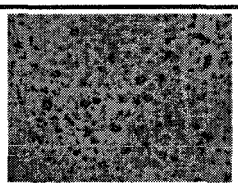
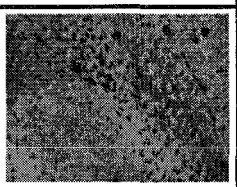
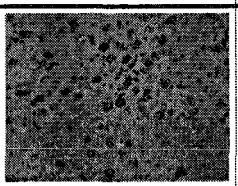
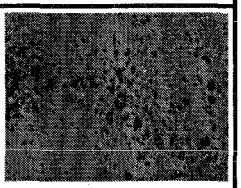
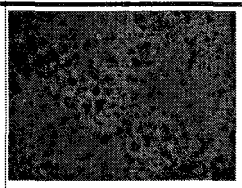
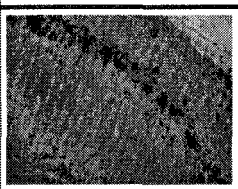
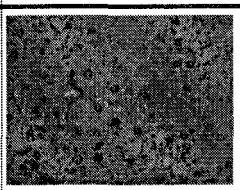
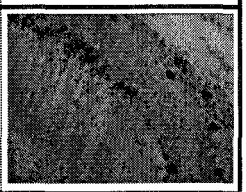
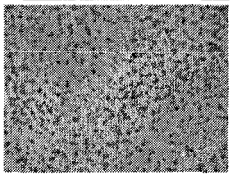
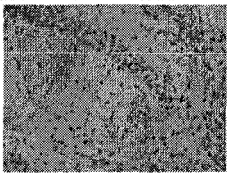
| Clone | Cortex | Hippocampus (CA1) | Clone | Cortex | Hippocampus (CA1) |
|---|---|---|---|---|---|
| 6C10F9 C12A11 |  |  | 6C10E5 E9C12 |  |  |
| 6H1A11 C11 |  |  | 6H1G6E 6 |  |  |
| 2B6A10 C11 |  |  | 2B6G7A 12 |  |  |
| 3A8A12 G7 |  |  | 3A8E12 H8 |  |  |
| 7C2(1) F10C10 D3 |  |  | 7C2(2) B9F11D 5 |  |  |
| ***Control*** AT100 antibody |  |  | ***Control*** PG5 antibody |  |  |
| ***Control*** No primary antibody |  |  | | | |

*FIGURE 1-1*

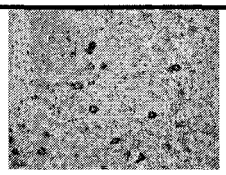
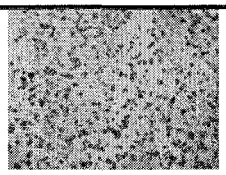
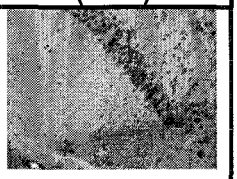
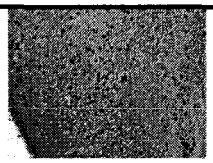
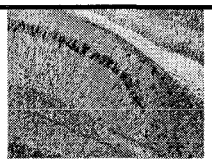
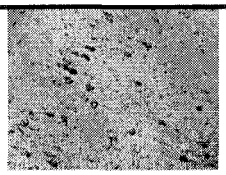
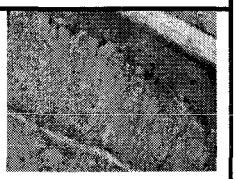
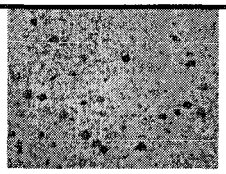
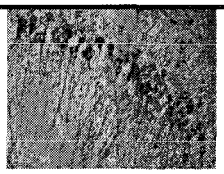
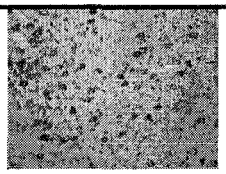
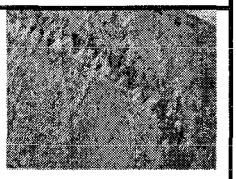
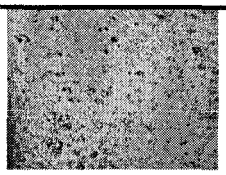
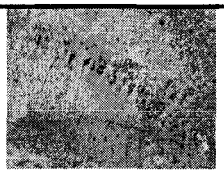
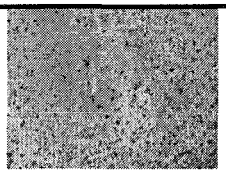
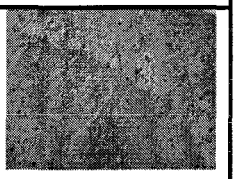
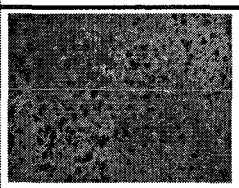
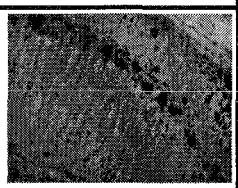
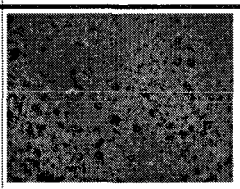
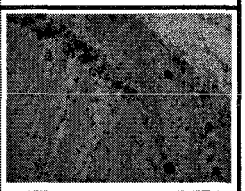
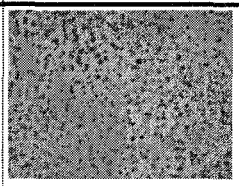
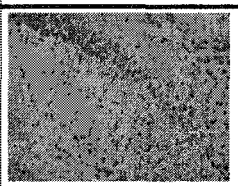
| Clone | Cortex | Hippocampus (CA1) | Clone | Cortex | Hippocampus (CA1) |
|---|---|---|---|---|---|
| A4-2A1-18 |  |  | A6-2G5-08 |  |  |
| A4-4A6-48 |  |  | A6-2G5-30 |  |  |
| A4-2A1-40 |  |  | A6-2G5-41 |  |  |
| A6-1D2-12 |  |  | A4-4A6-18 |  |  |
| ***Control*** AT100 antibody |  |  | ***Control*** PG5 antibody |  |  |
| ***Control*** No primary antibody |  |  | | | |

*FIGURE 1-2*

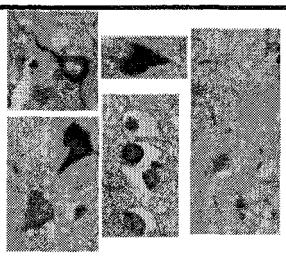
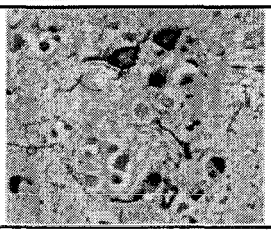
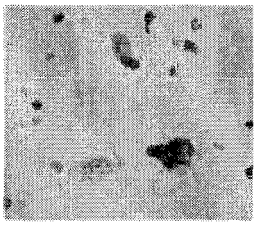
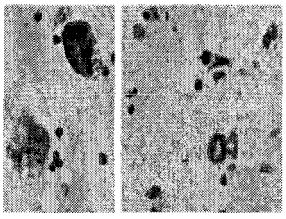
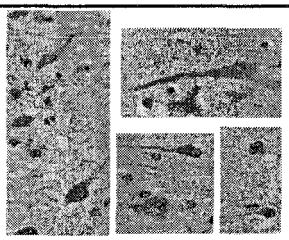
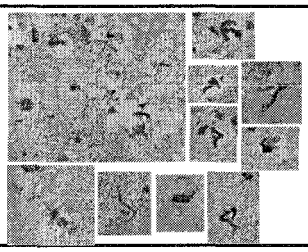
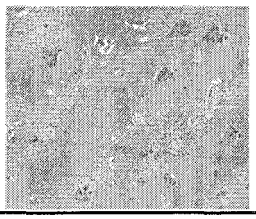
| Diagnosis | Region | ACI-3A8-Ab1 TAUPIR staining |
|---|---|---|
| AD | Hippocampus |  |
| FAD | Anterior hippocampus |  |
| AGD | Anterior hippocampus |  |
| PSP | Pallidum |  |
| FTDP-17 | Frontal cortex |  |
| CBD | Frontal cortex |  |
| Healthy control | Hippocampus |  |

FIGURE 2

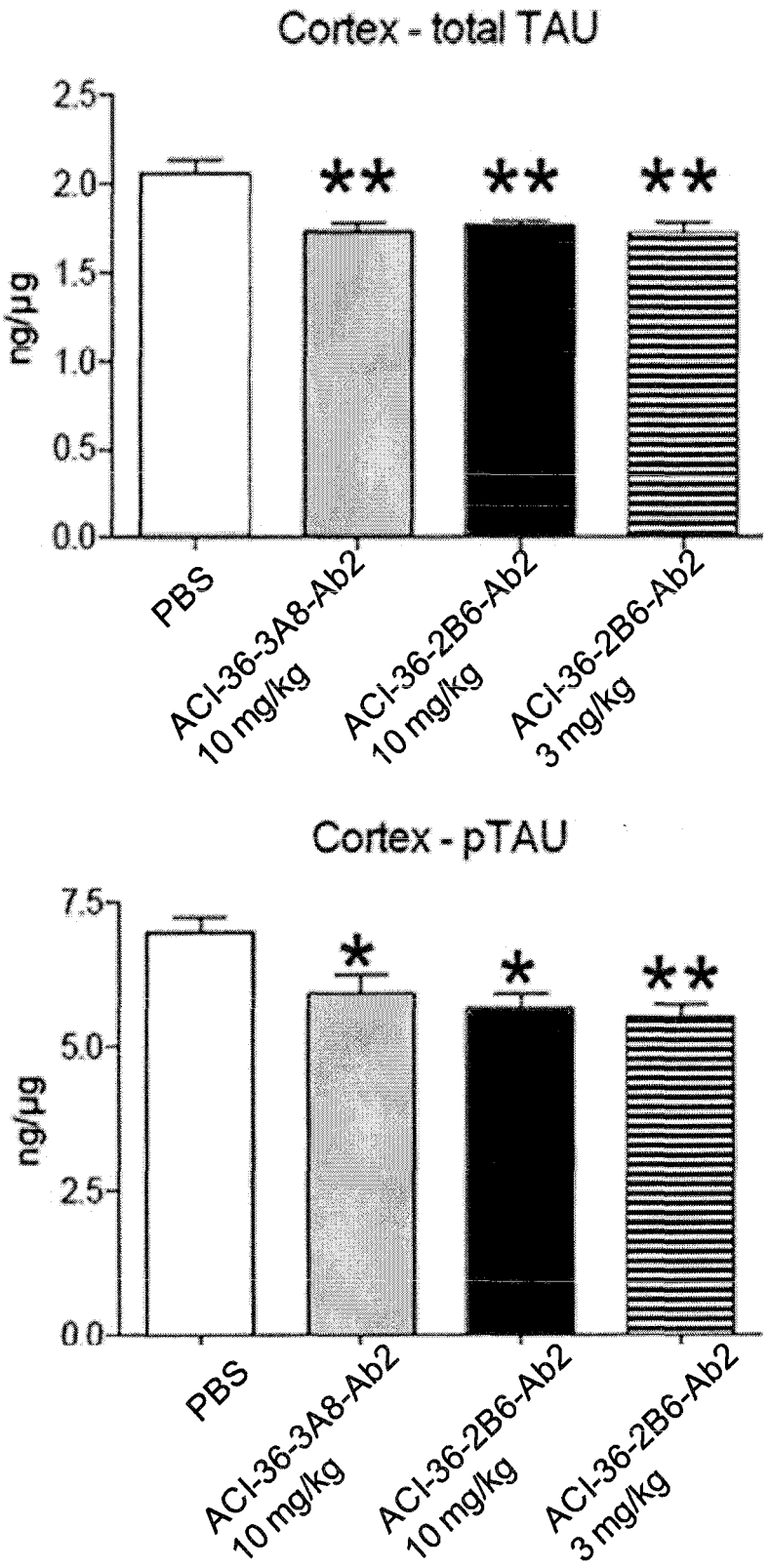

Cortex - total TAU
ng/ng
2.5
2.0
1.5
1.0
0.5
0.0
**
**
**
PBS
ACI-36-3A8-Ab2 10 mg/kg
ACI-36-2B6-Ab2 10 mg/kg
ACI-36-2B6-Ab2 3 mg/kg
Cortex - pTAU
ng/ng
7.5
5.0
2.5
0.0
*
*
**
PBS
ACI-36-3A8-Ab2 10 mg/kg
ACI-36-2B6-Ab2 10 mg/kg
ACI-36-2B6-Ab2 3 mg/kg

*FIGURE 3*

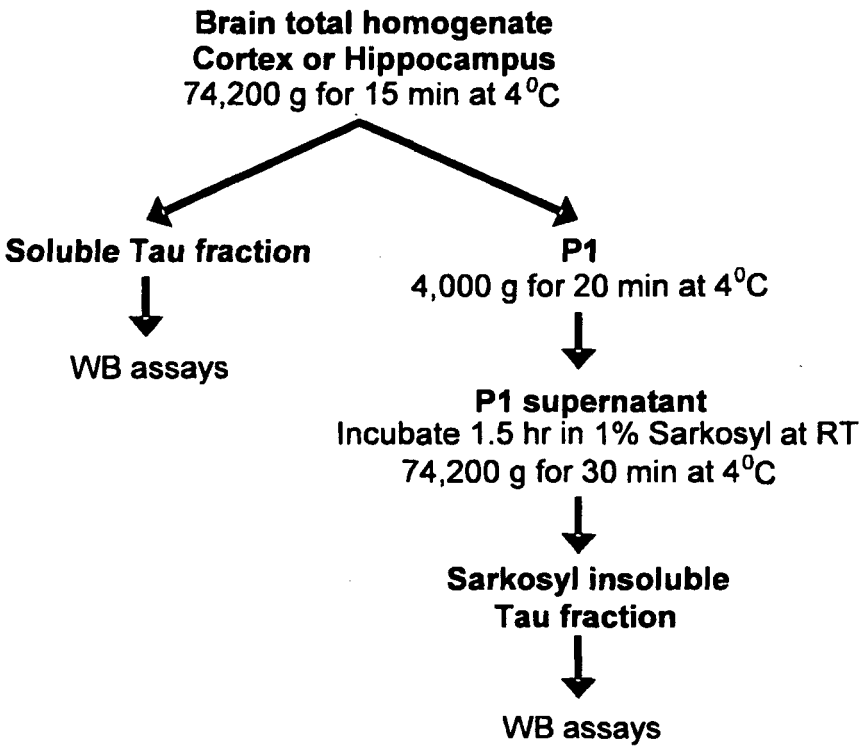



*FIGURE 4-1*

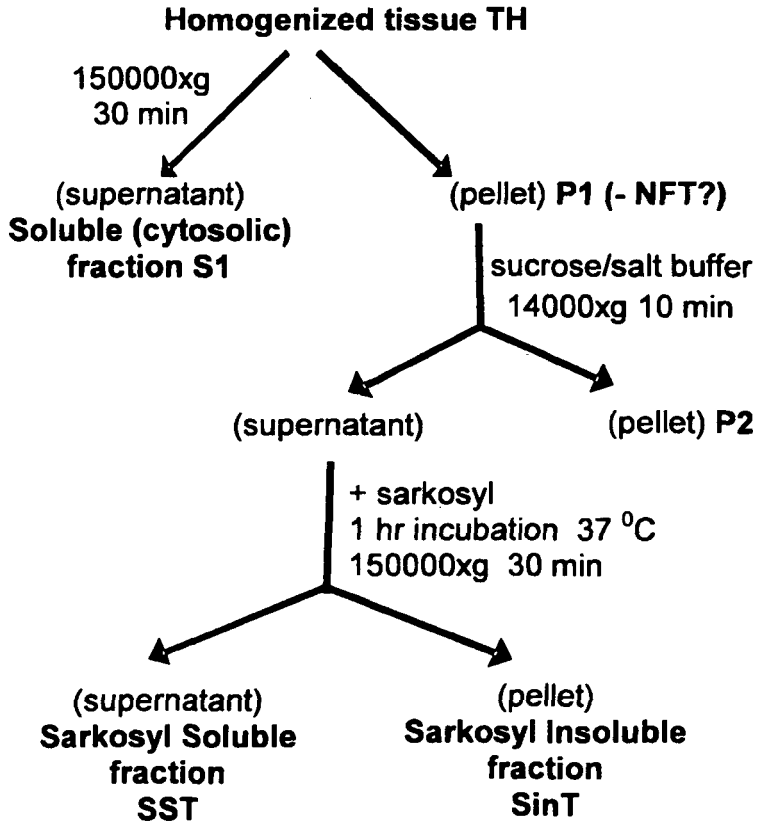



*FIGURE 4-2*

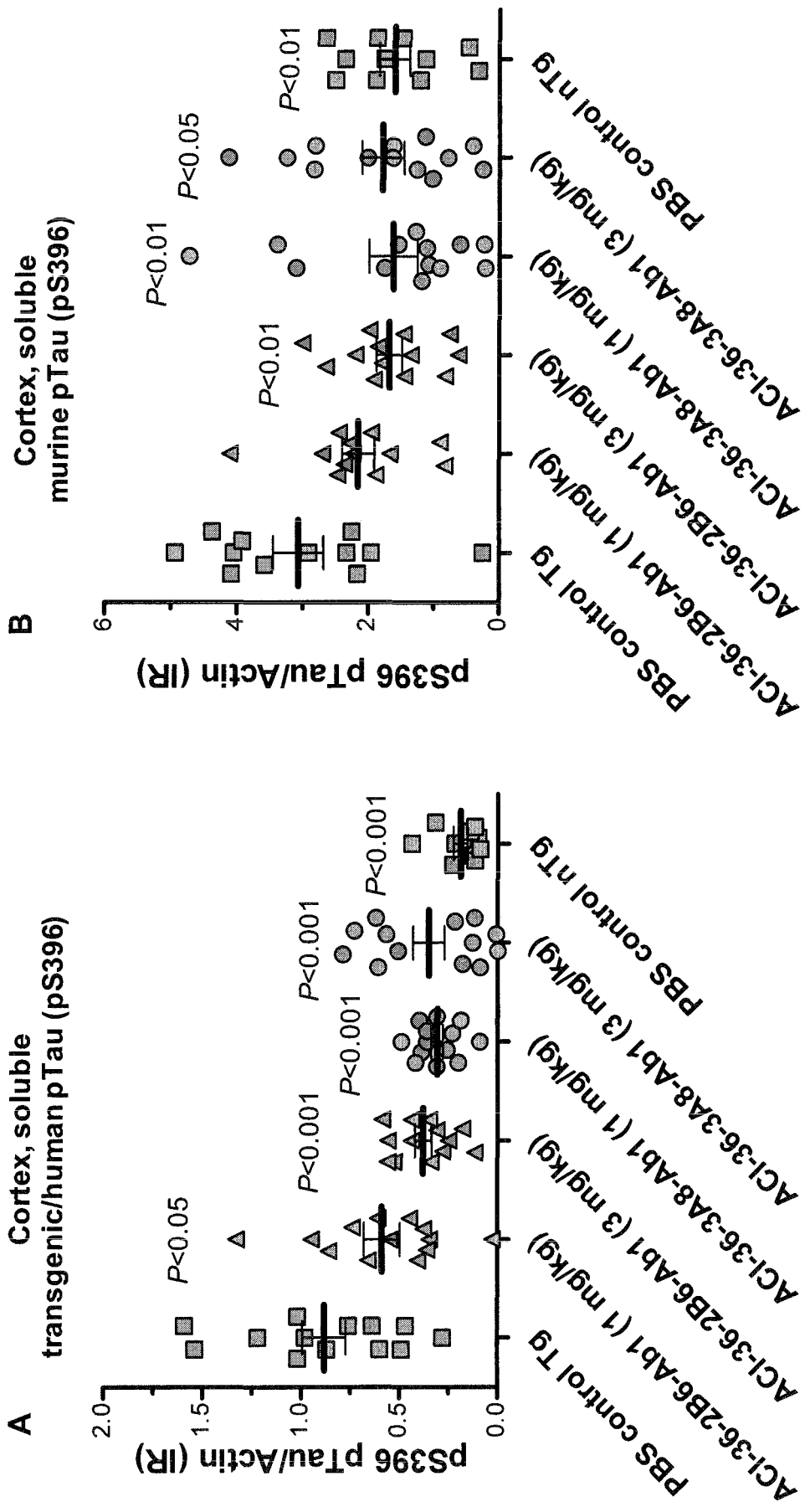

A
Cortex, soluble
transgenic/human pTau (pS396)
pS396 pTau/Actin (IR)
2.0
1.5
1.0
0.5
0.0
P<0.05
P<0.001
P<0.001
P<0.001
P<0.001
PBS control nTg
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)
B
Cortex, soluble
murine pTau (pS396)
pS396 pTau/Actin (IR)
6
4
2
0
P<0.01
P<0.05
P<0.01
P<0.01
P<0.01
PBS control nTg
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)
PBS control Tg

FIGURE 5-1

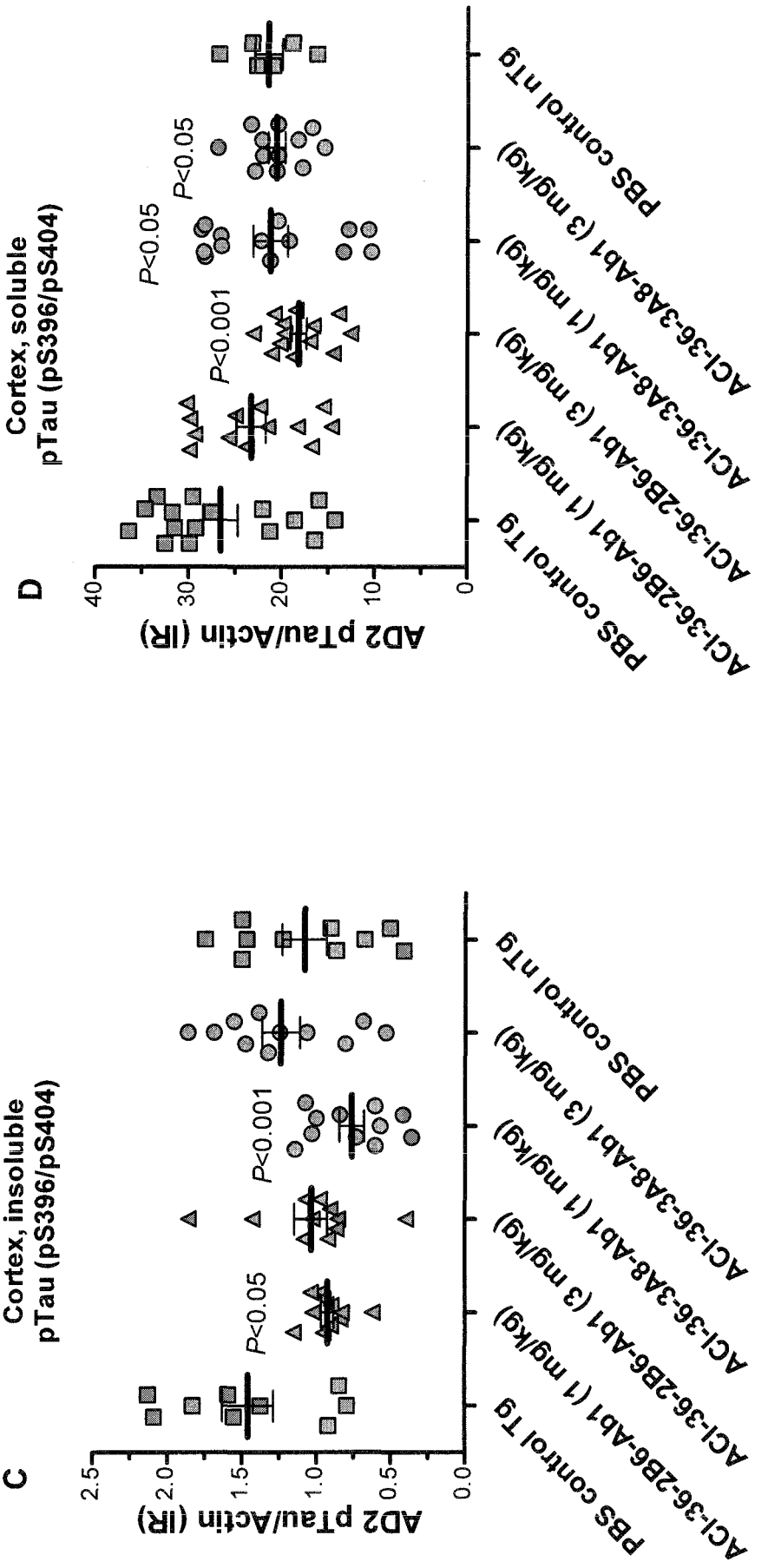

C
Cortex, insoluble
pTau (pS396/pS404)
AD2 pTau/Actin (IR)
2.5
2.0
1.5
1.0
0.5
0.0
P<0.05
P<0.001
PBS control nTg
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)
PBS control Tg
D
Cortex, soluble
pTau (pS396/pS404)
AD2 pTau/Actin (IR)
40
30
20
10
0
P<0.05
P<0.001
P<0.05
PBS control nTg
ACI-36-3A8-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-2B6-Ab1 (1 mg/kg)
PBS control Tg

FIGURE 5-2

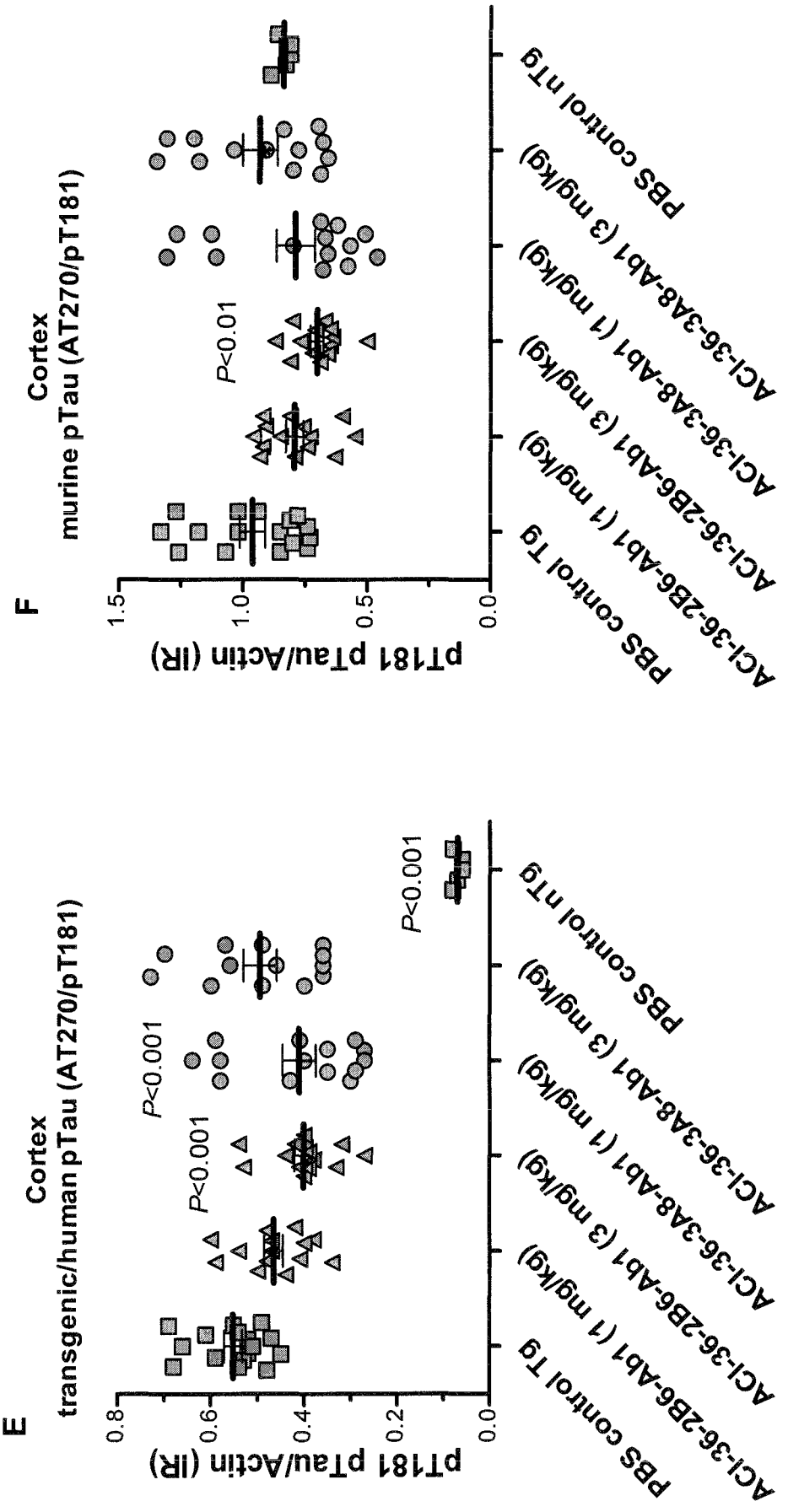

E
Cortex
transgenic/human pTau (AT270/pT181)
pT181 pTau/Actin (IR)
0.0
0.2
0.4
0.6
0.8
P<0.001
P<0.001
P<0.001
PBS control nTg
PBS control Tg
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)
F
Cortex
murine pTau (AT270/pT181)
pT181 pTau/Actin (IR)
0.0
0.5
1.0
1.5
P<0.01
PBS control nTg
PBS control Tg
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

FIGURE 5-3

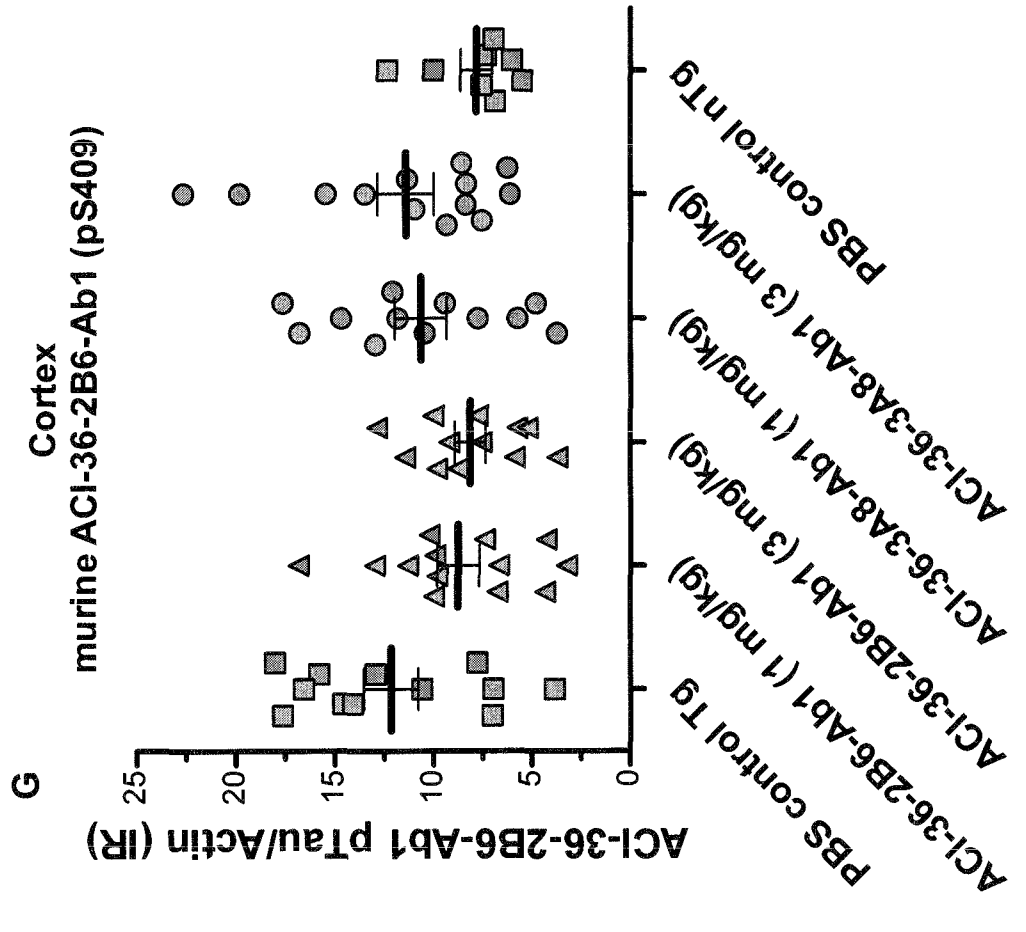

G
Cortex
murine ACI-36-2B6-Ab1 (pS409)
ACI-36-2B6-Ab1 pTau/Actin (IR)
25
20
15
10
5
0
PBS control TG
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)
PBS control nTg

FIGURE 5-4

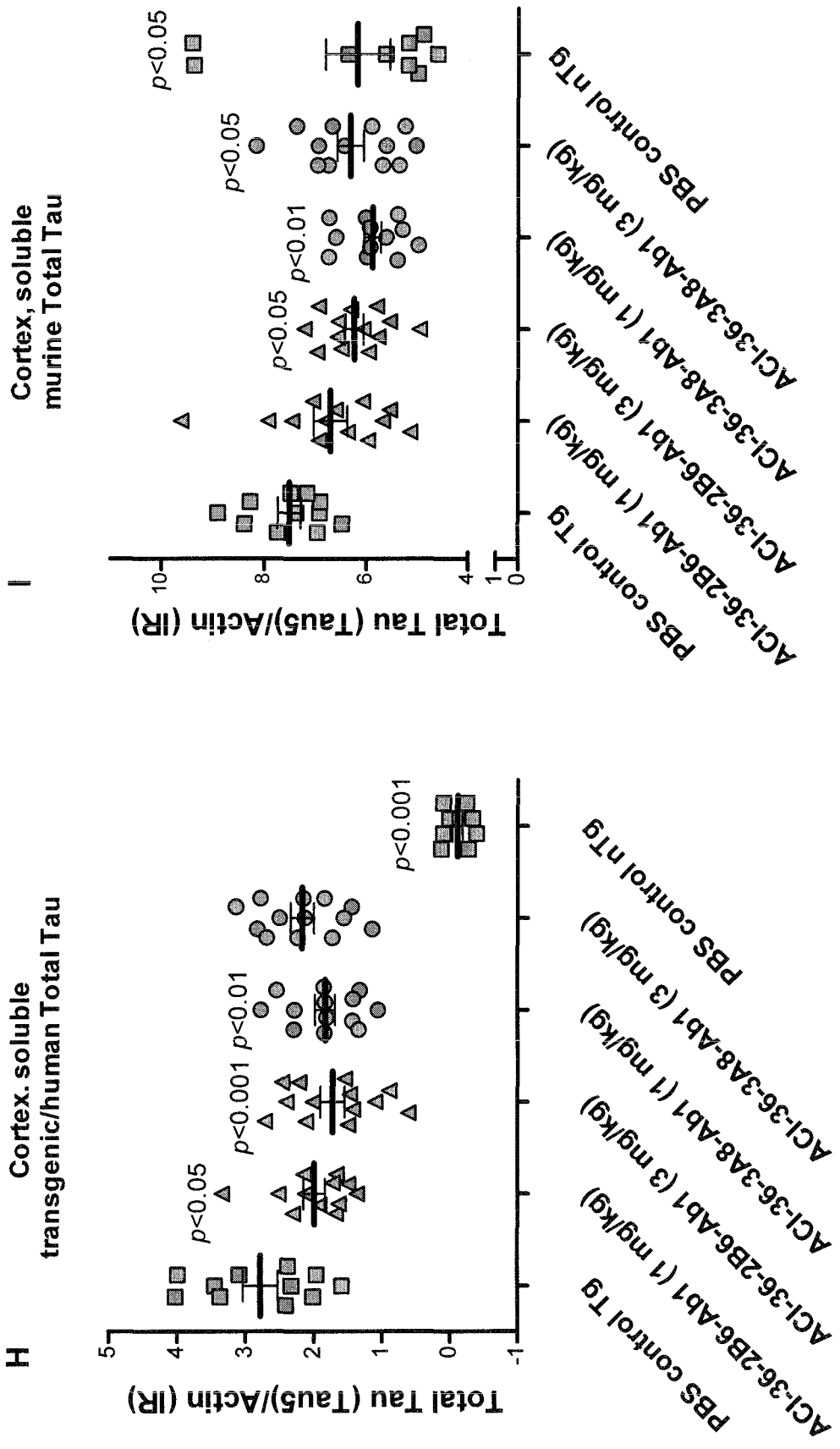

H
Cortex. soluble
transgenic/human Total Tau
Total Tau (Tau5)/Actin (IR)
p<0.05
p<0.001
p<0.01
p<0.001
PBS control nTg
PBS control Tg
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)
I
Cortex, soluble
murine Total Tau
Total Tau (Tau5)/Actin (IR)
p<0.05
p<0.05
p<0.01
p<0.05
PBS control nTg
PBS control Tg
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

*FIGURE 5-5*

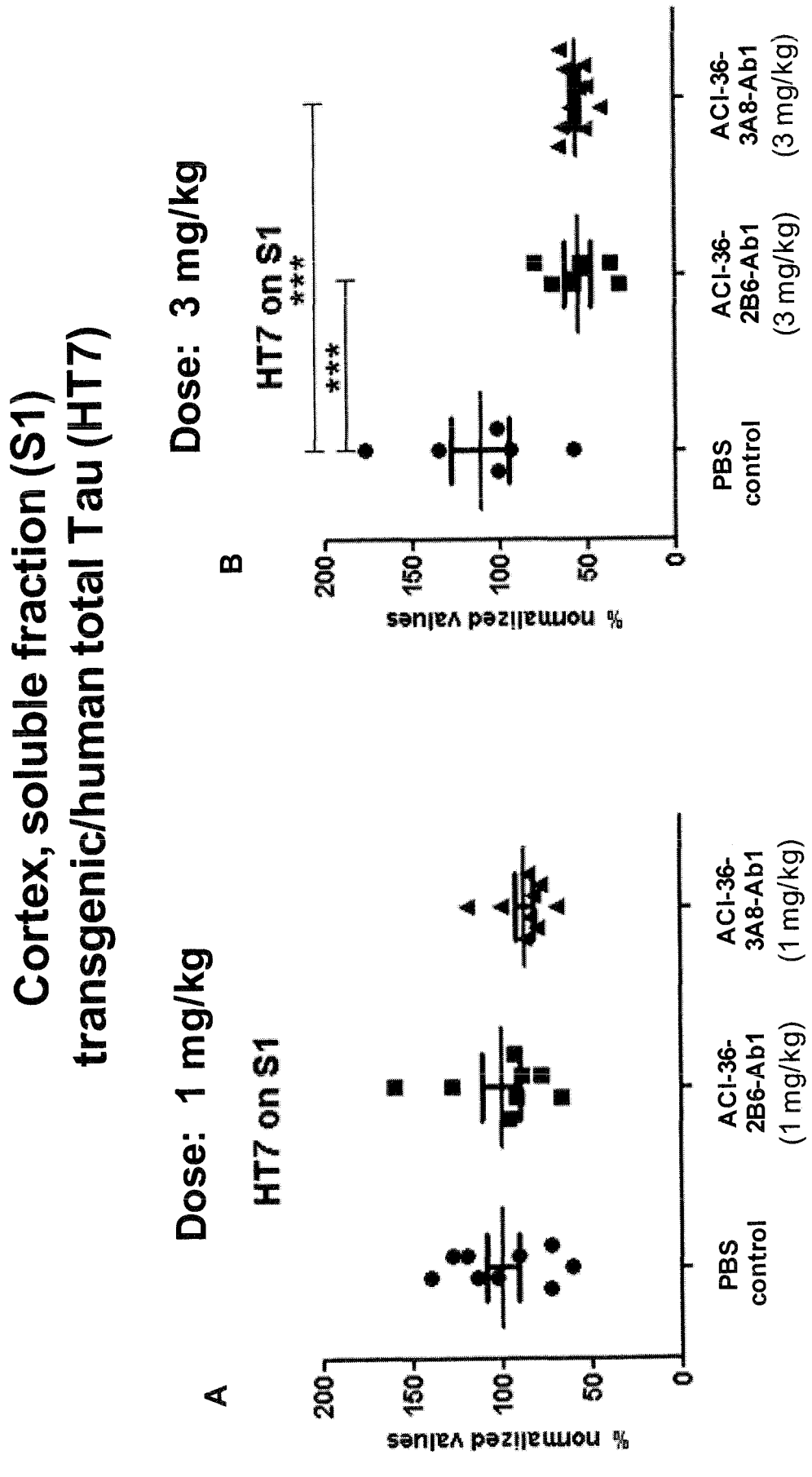

Cortex, soluble fraction (S1)
transgenic/human total Tau (HT7)
A
Dose: 1 mg/kg
HT7 on S1
% normalized values
200
150
100
50
0
PBS control
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
B
Dose: 3 mg/kg
HT7 on S1
***
***
% normalized values
200
150
100
50
0
PBS control
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

FIGURE 6-1

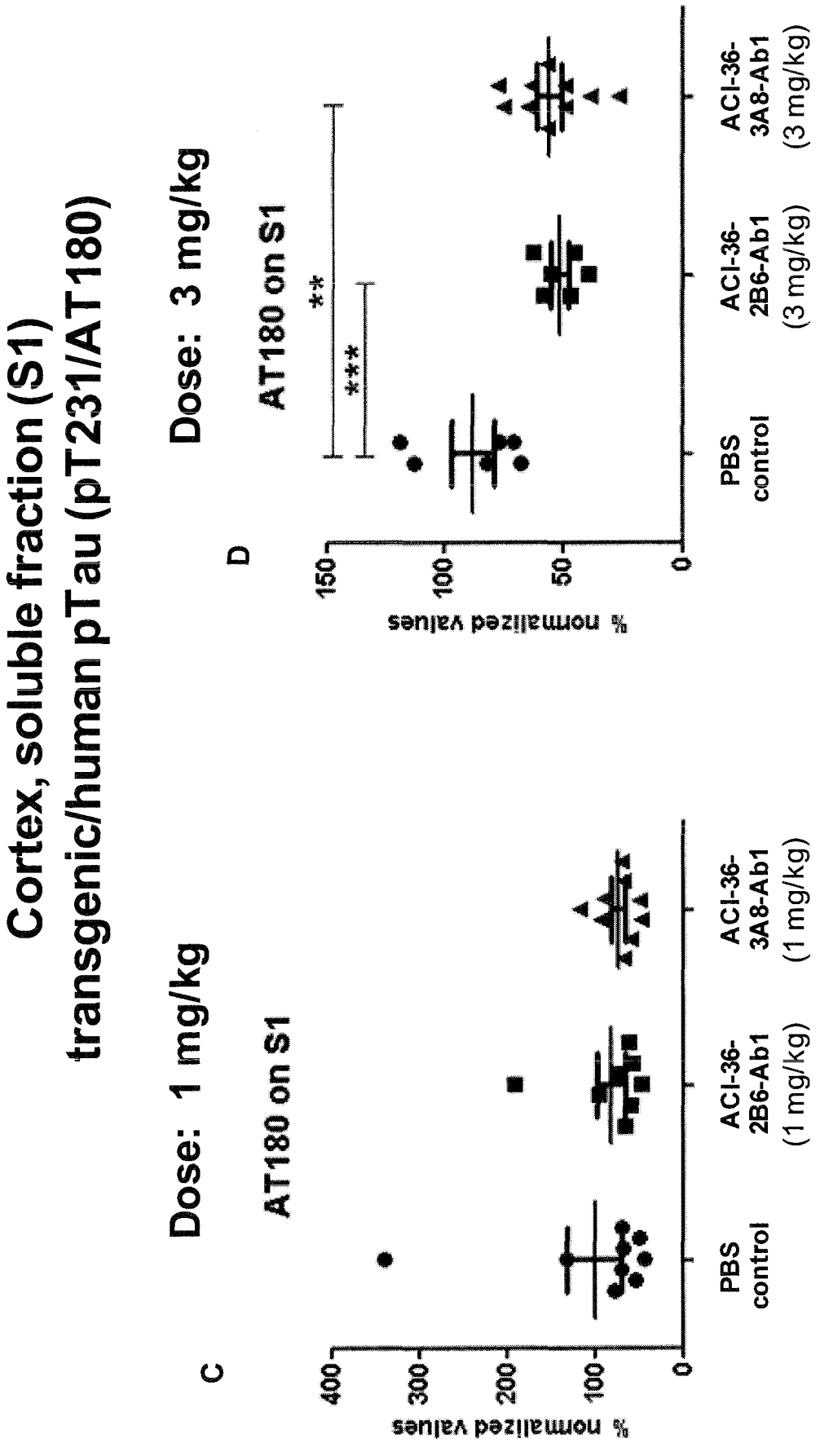

Cortex, soluble fraction (S1)
transgenic/human pTau (pT231/AT180)
C
Dose: 1 mg/kg
AT180 on S1
% normalized values
400
300
200
100
0
PBS control
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
D
Dose: 3 mg/kg
AT180 on S1
**
***
% normalized values
150
100
50
0
PBS control
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

*FIGURE 6-2*

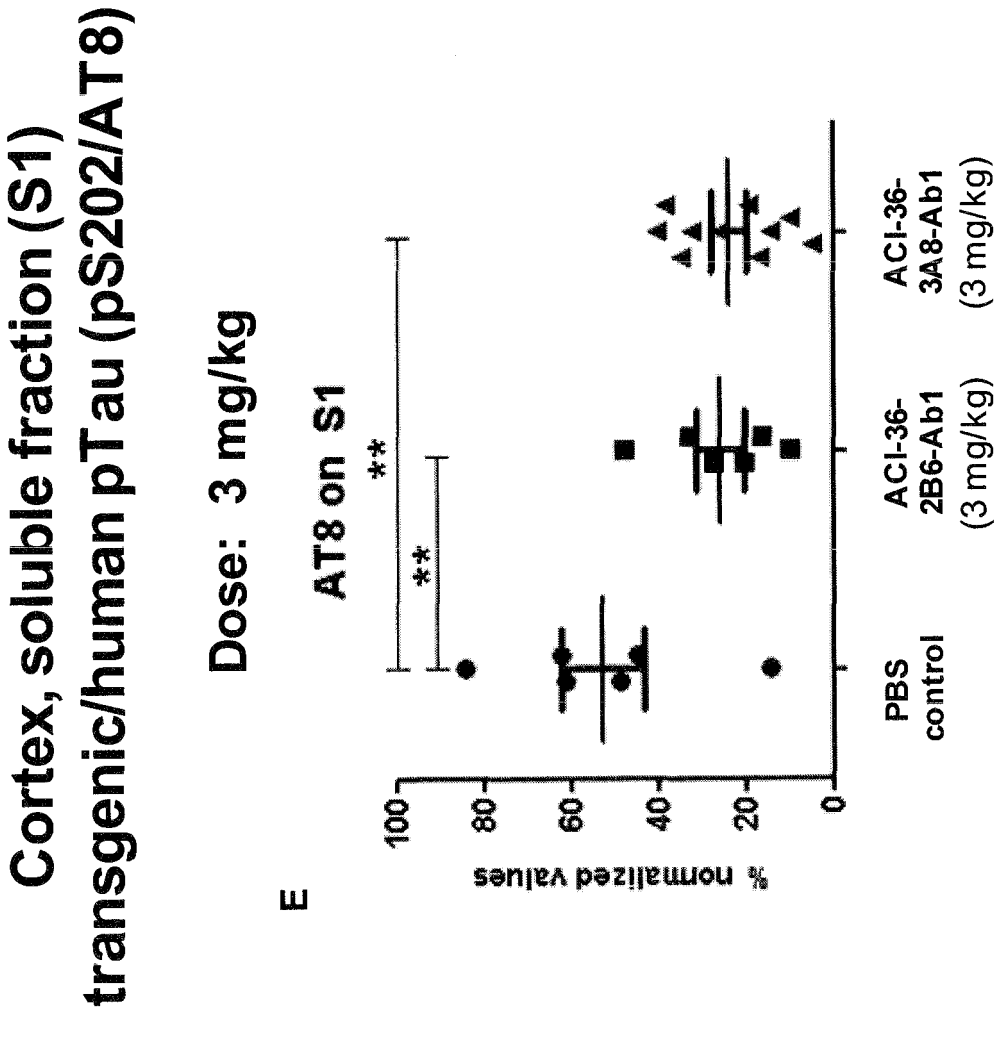

Cortex, soluble fraction (S1)
transgenic/human pTau (pS202/AT8)
Dose: 3 mg/kg
E
AT8 on S1
**
**
% normalized values
100
80
60
40
20
0
PBS control
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

*FIGURE 6-3*

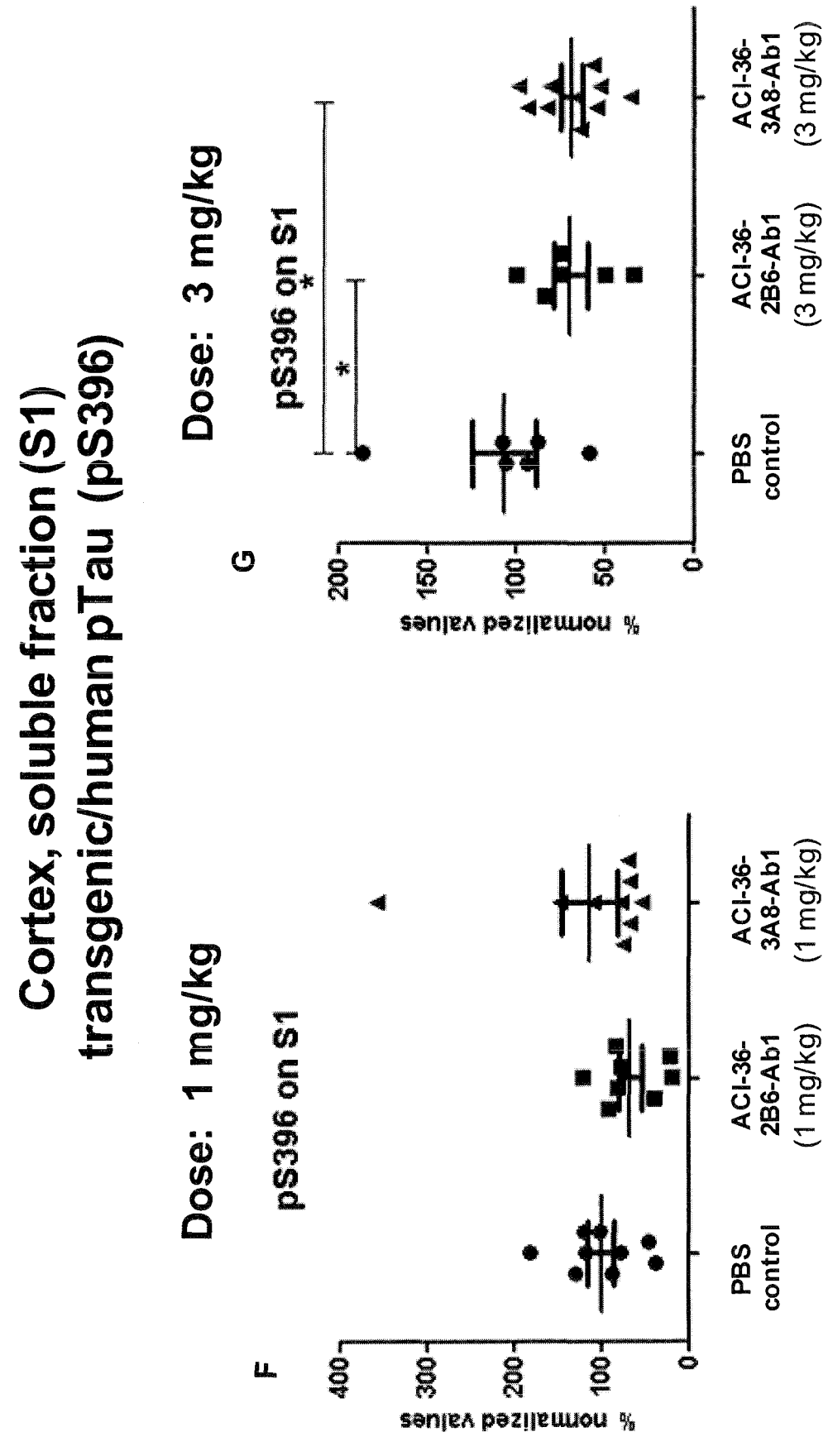

Cortex, soluble fraction (S1)
transgenic/human pTau (pS396)
F
Dose: 1 mg/kg
pS396 on S1
% normalized values
400
300
200
100
0
PBS control
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
G
Dose: 3 mg/kg
pS396 on S1
*
*
% normalized values
200
150
100
50
0
PBS control
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

FIGURE 6-4

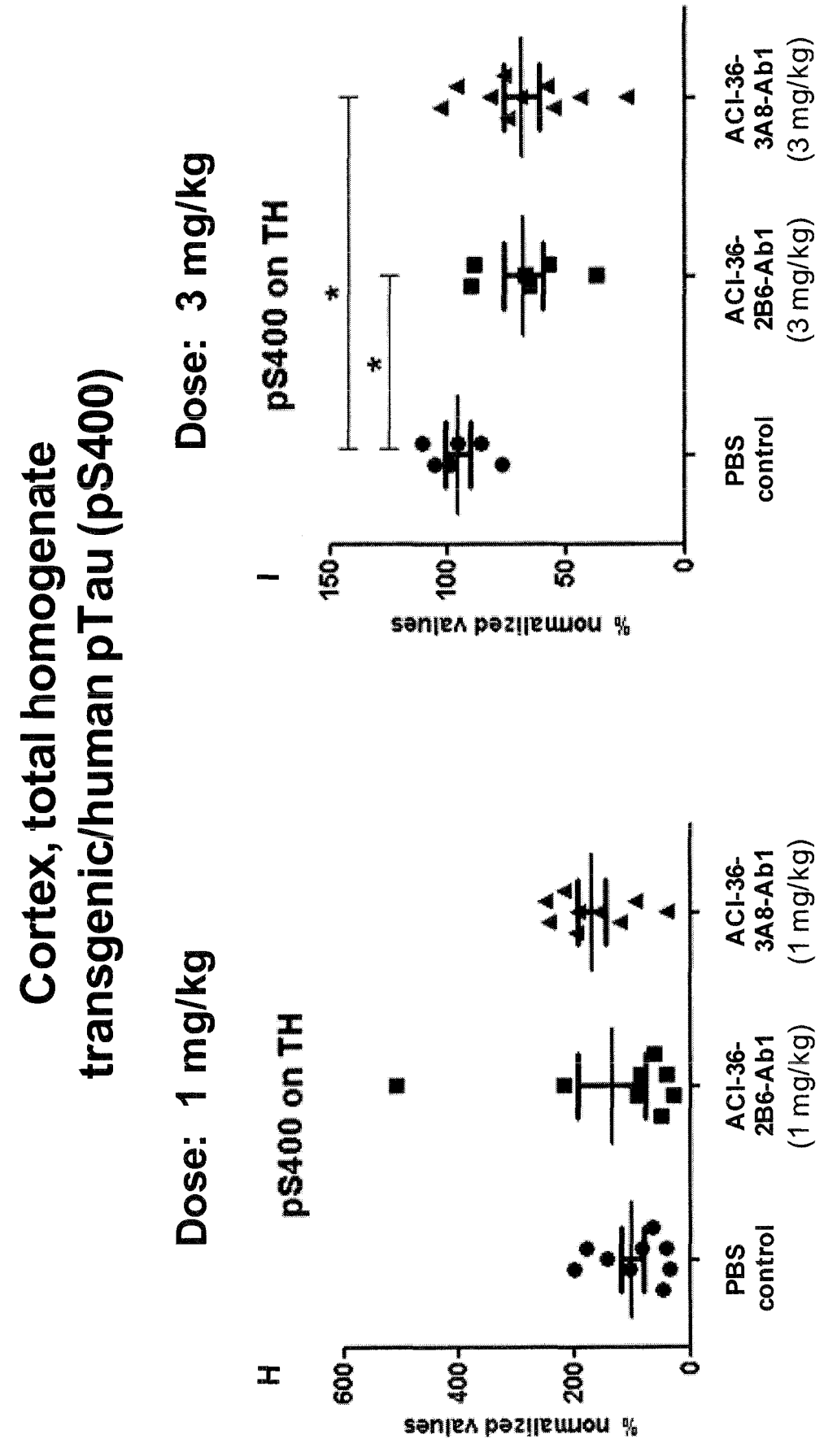

Cortex, total homogenate
transgenic/human pTau (pS400)
Dose: 1 mg/kg
Dose: 3 mg/kg
H
I
pS400 on TH
pS400 on TH
% normalized values
% normalized values
600
400
200
0
150
100
50
0
*
*
PBS control
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
PBS control
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

FIGURE 6-5

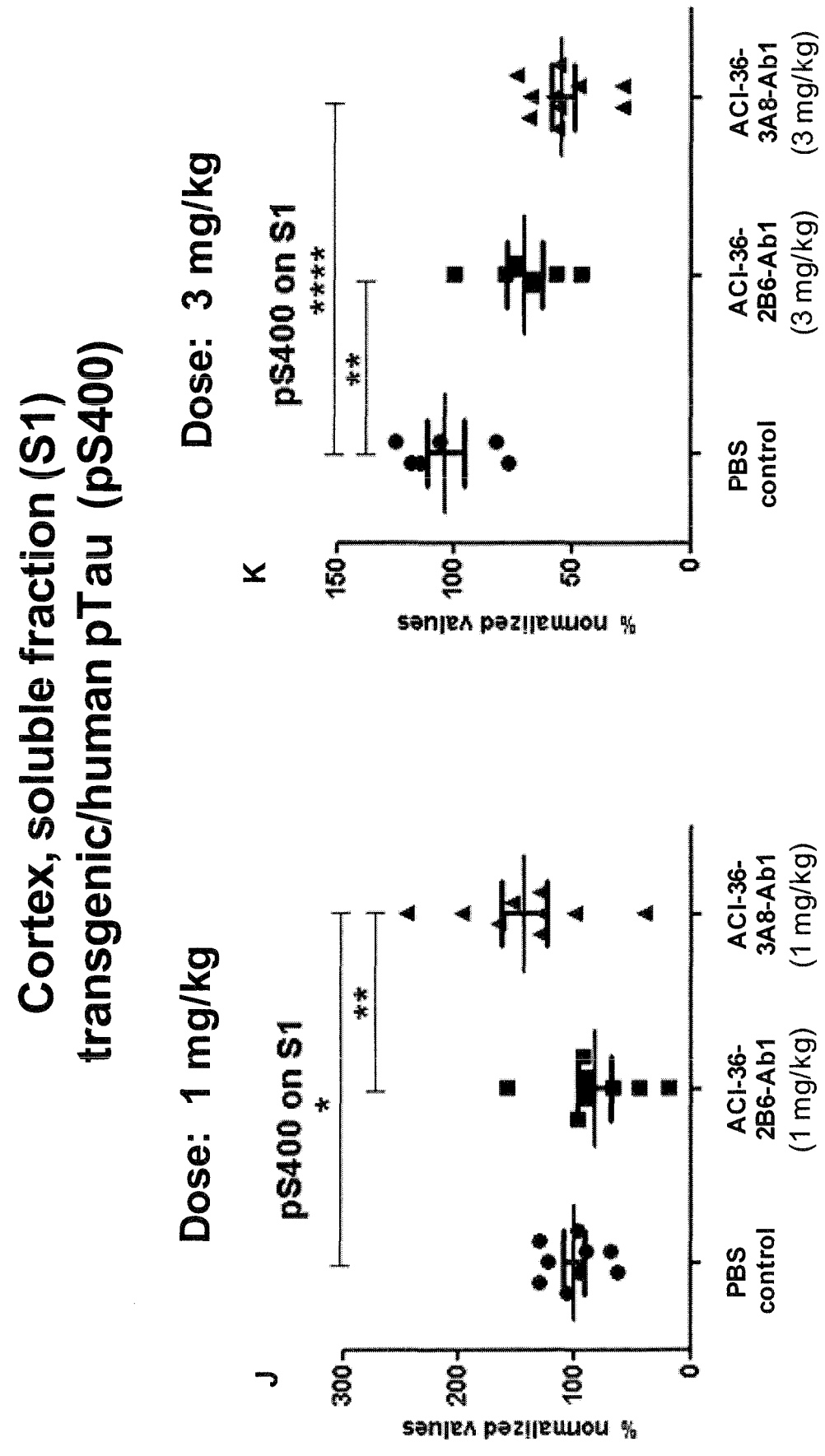

Cortex, soluble fraction (S1)
transgenic/human pTau (pS400)
Dose: 1 mg/kg
pS400 on S1
J
% normalized values
300
200
100
0
*
**
PBS control
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
Dose: 3 mg/kg
pS400 on S1
K
% normalized values
150
100
50
0
**
****
PBS control
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

*FIGURE 6-6*

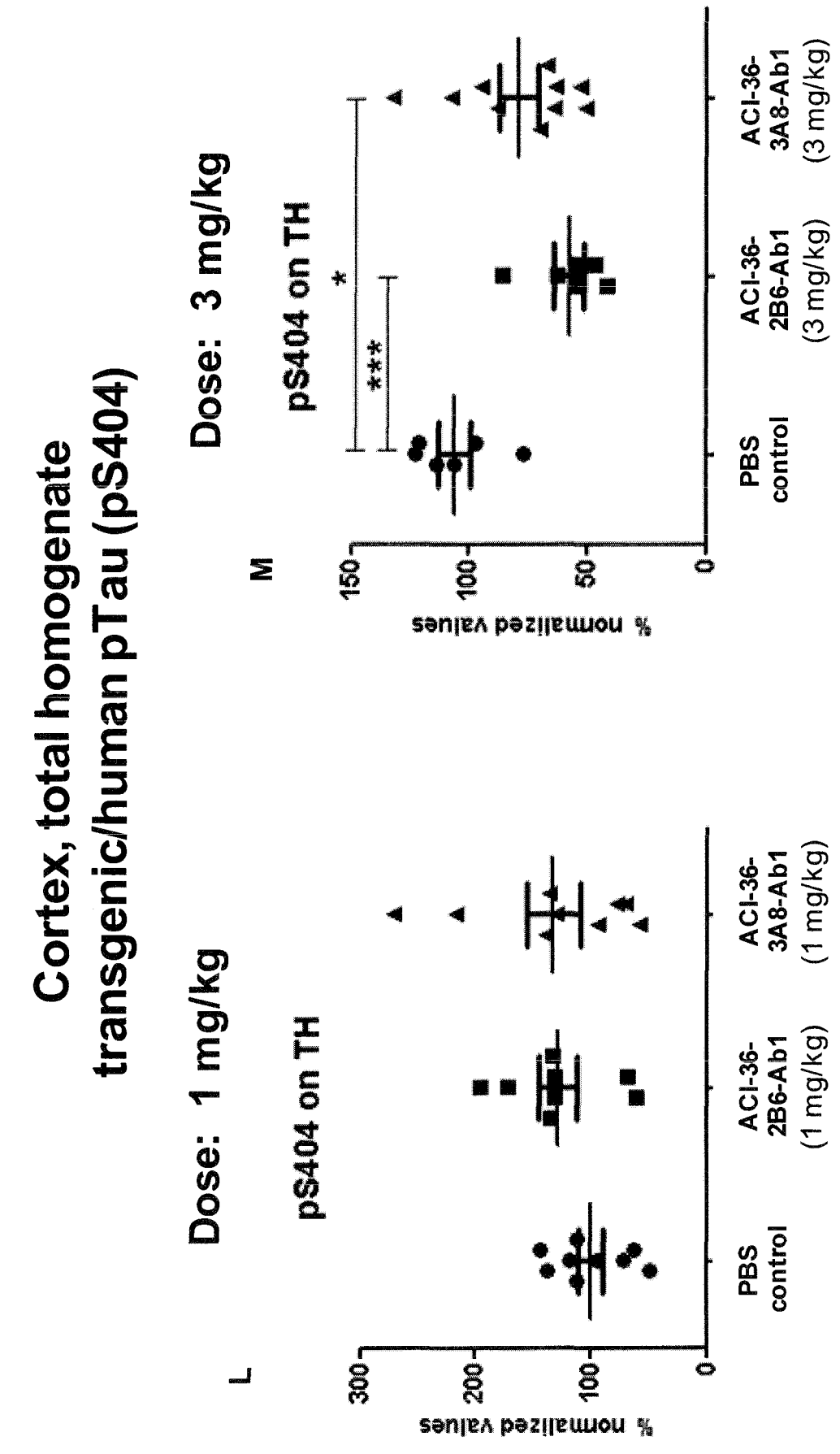

Cortex, total homogenate
transgenic/human pTau (pS404)
Dose: 1 mg/kg
pS404 on TH
L
% normalized values
300
200
100
0
PBS control
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
Dose: 3 mg/kg
pS404 on TH
M
% normalized values
150
100
50
0
***
*
PBS control
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

*FIGURE 6-7*

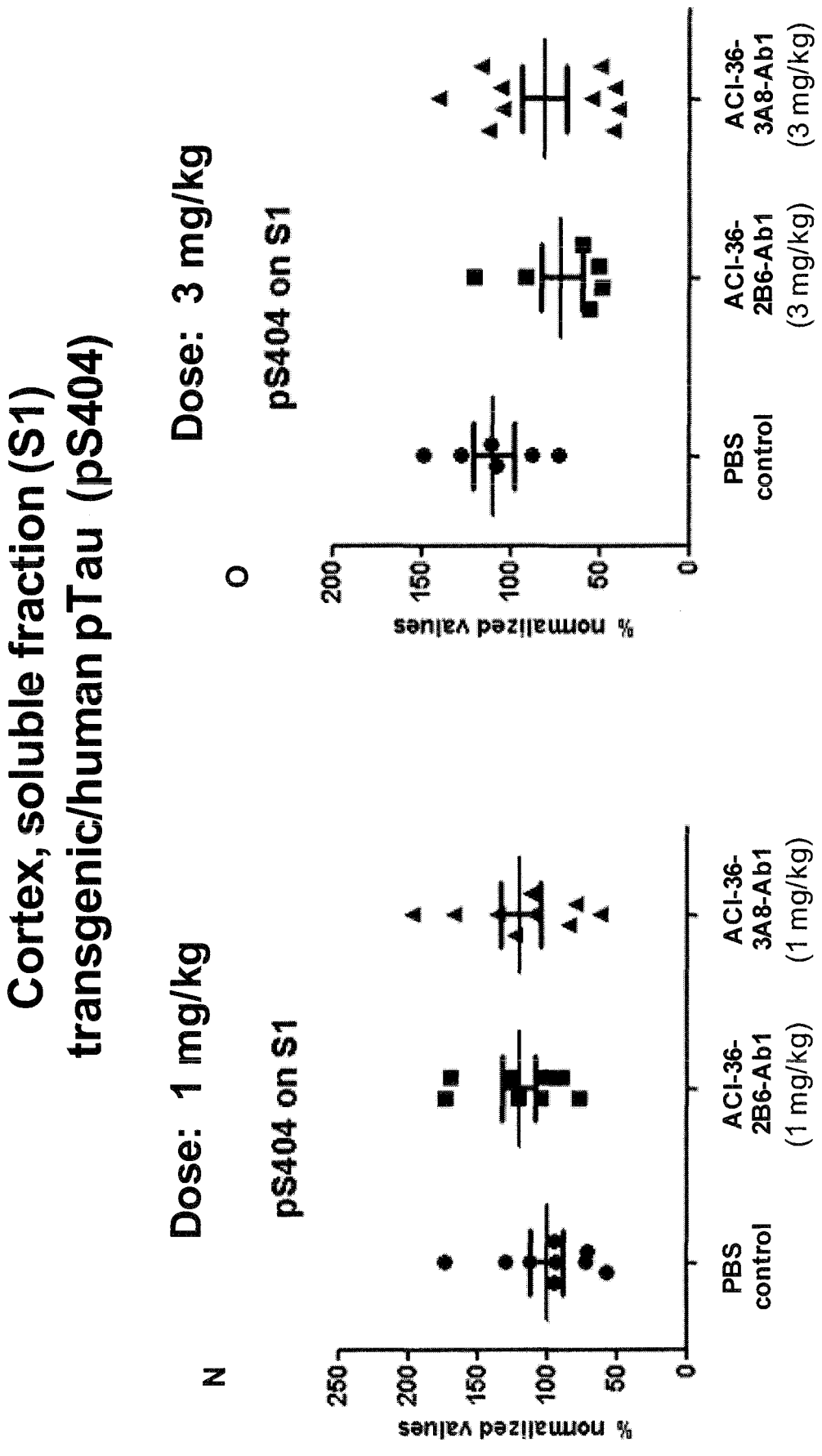

Cortex, soluble fraction (S1)
transgenic/human pTau (pS404)
N
Dose: 1 mg/kg
pS404 on S1
% normalized values
250
200
150
100
50
0
PBS control
ACI-36-2B6-Ab1 (1 mg/kg)
ACI-36-3A8-Ab1 (1 mg/kg)
O
Dose: 3 mg/kg
pS404 on S1
% normalized values
200
150
100
50
0
PBS control
ACI-36-2B6-Ab1 (3 mg/kg)
ACI-36-3A8-Ab1 (3 mg/kg)

*FIGURE 6-8*

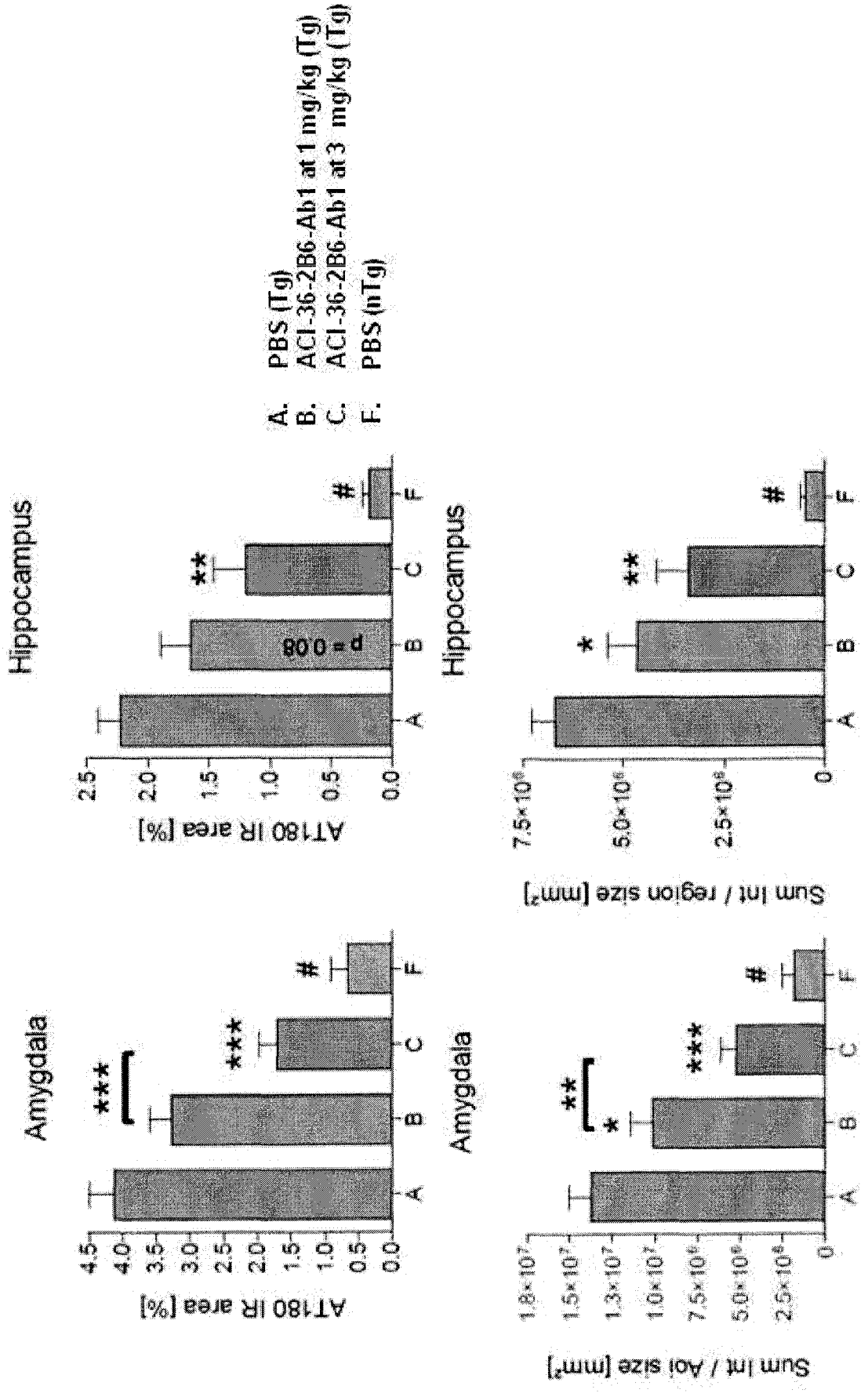

A. PBS (Tg)
B. ACI-36-2B6-Ab1 at 1 mg/kg (Tg)
C. ACI-36-2B6-Ab1 at 3 mg/kg (Tg)
F. PBS (nTg)
Hippocampus
AT180 IR area [%]
p = 0.08
Amygdala
AT180 IR area [%]
Hippocampus
Sum Int / region size [mm²]
Amygdala
Sum Int / Aoi size [mm²]

FIGURE 7

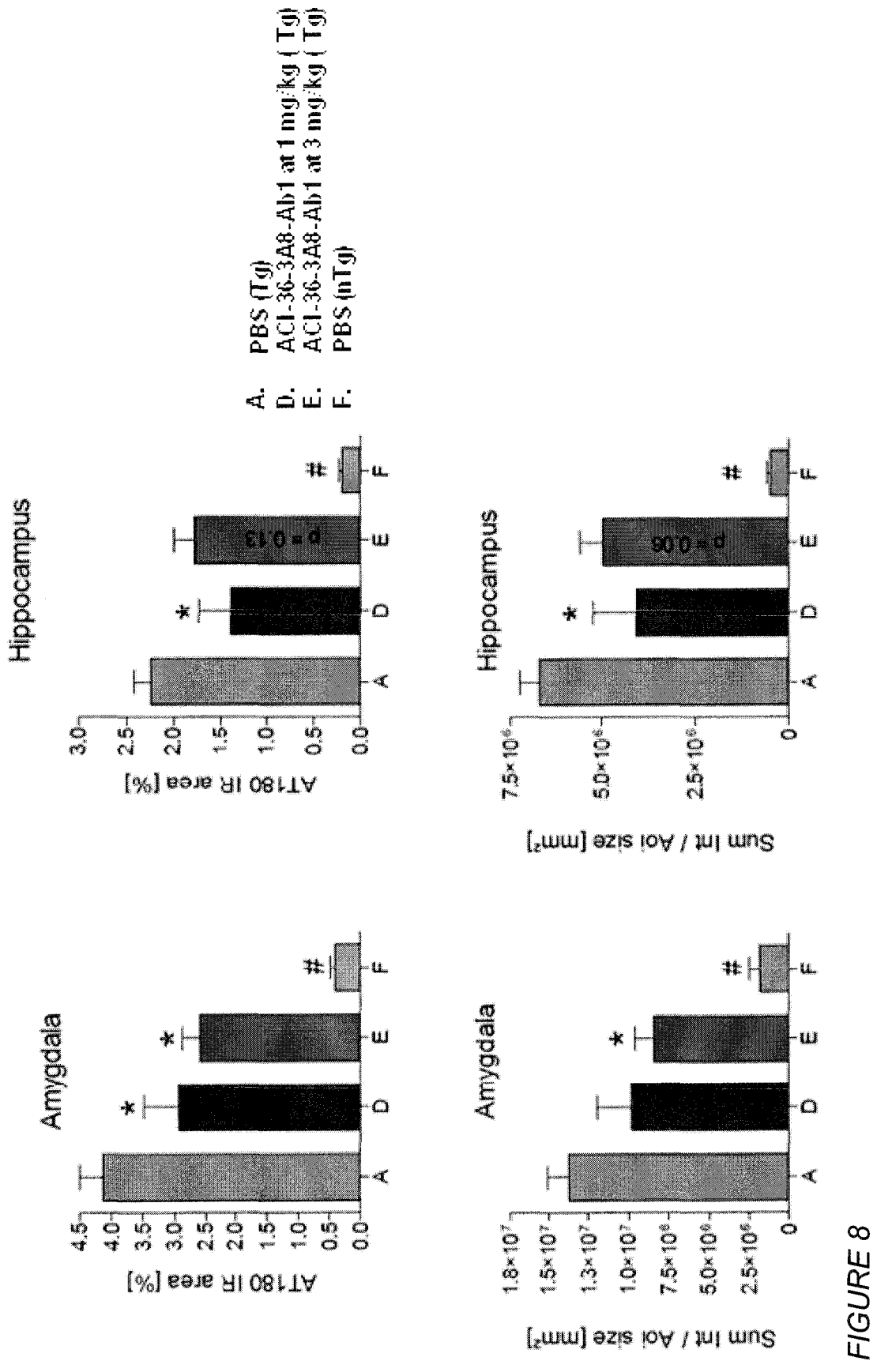
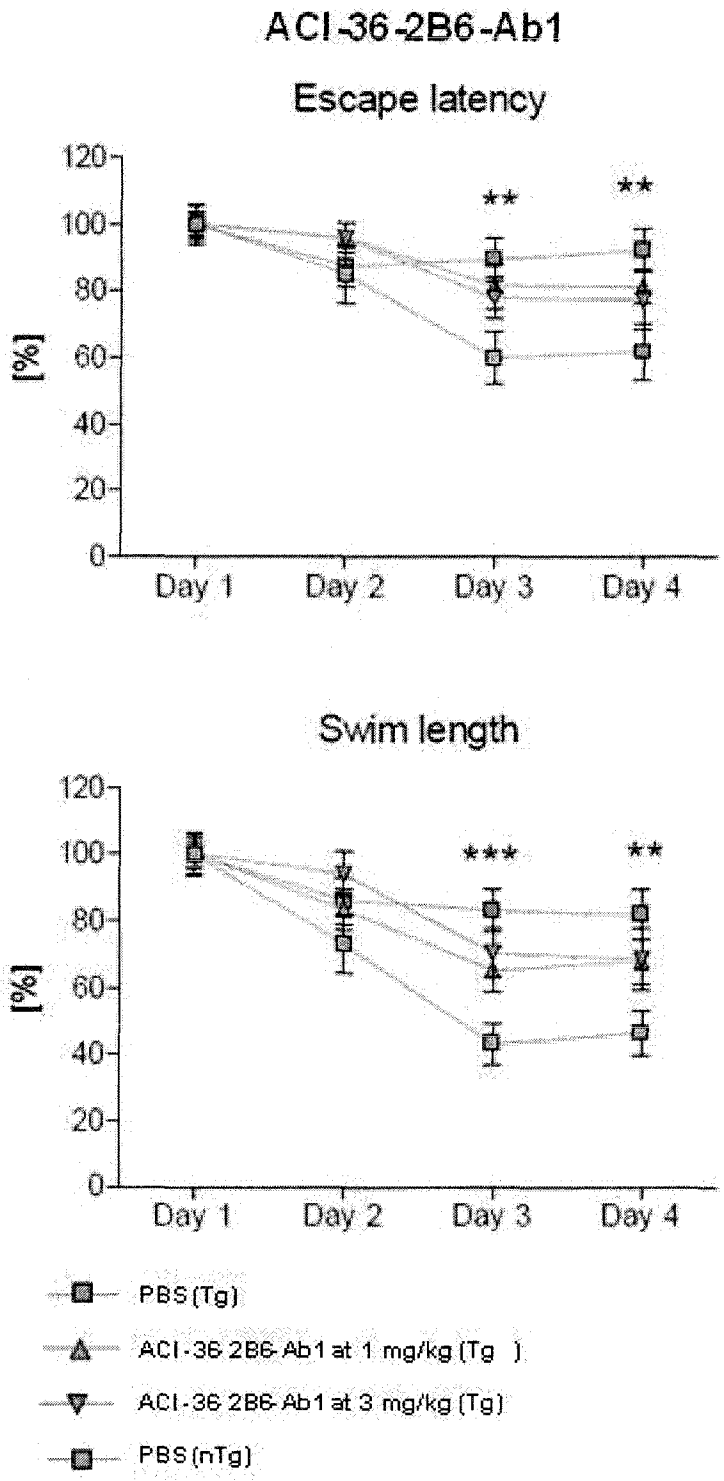
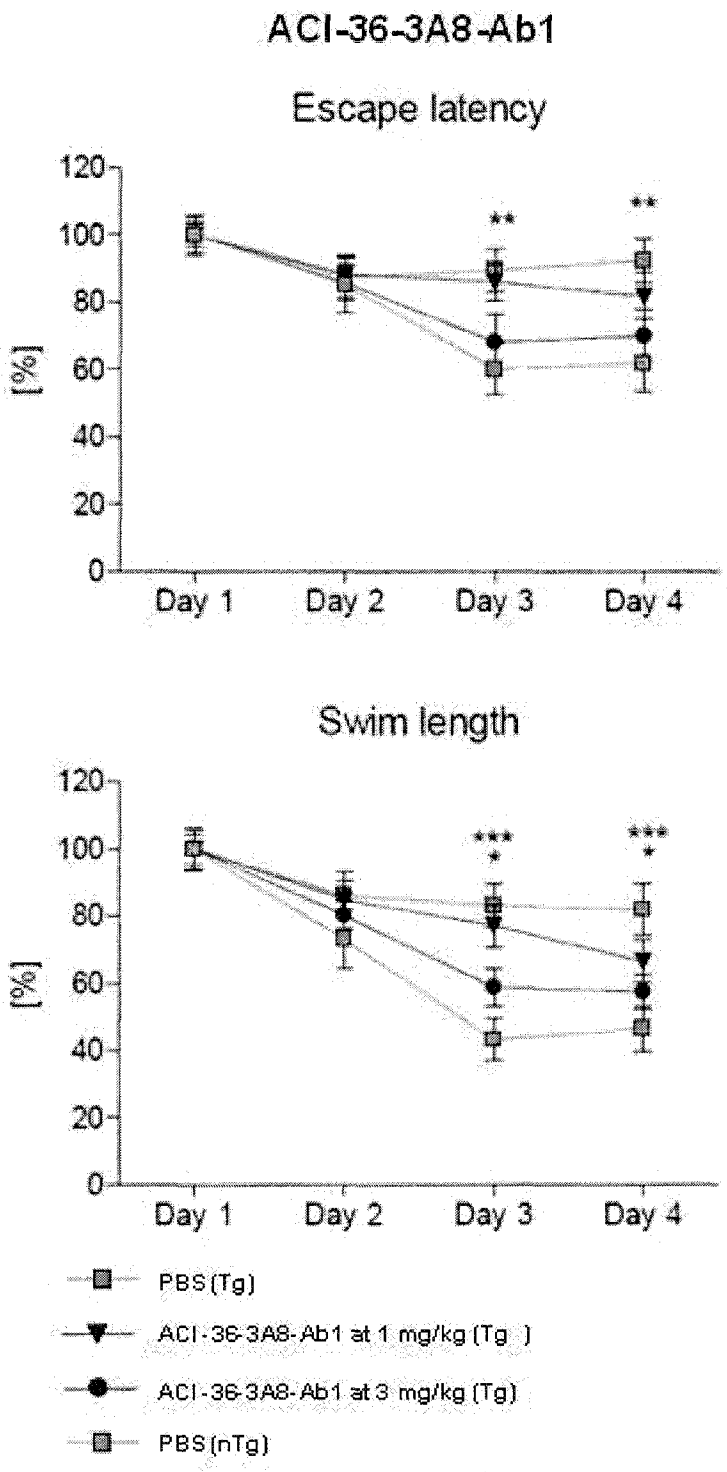

A. PBS (Tg)
D. ACI-36-3A8-Ab1 at 1 mg/kg (Tg)
E. ACI-36-3A8-Ab1 at 3 mg/kg (Tg)
F. PBS (nTg)
Hippocampus
AT180 IR area [%]
p = 0.13
Hippocampus
Sum Int / Aoi size [mm²]
p = 0.06
Amygdala
AT180 IR area [%]
Amygdala
Sum Int / Aoi size [mm²]

FIGURE 8




| | Escape latency | | | Swim length | | |
|---|---|---|---|---|---|---|
| | Day 2 | Day 3 | Day 4 | Day 2 | Day 3 | Day 4 |
| A vs B | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 |
| A vs C | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 |
| A vs F | P > 0.05 | P<0.01 | P<0.01 | P > 0.05 | P<0.001 | P<0.01 |

*FIGURE 9*




| | Escape latency | | | Swim length | | |
|---|---|---|---|---|---|---|
| | Day 2 | Day 3 | Day 4 | Day 2 | Day 3 | Day 4 |
| A vs D | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 |
| A vs E | P > 0.05 | P > 0.05 | P > 0.05 | P > 0.05 | P < 0.05 | P < 0.05 |
| A vs F | P > 0.05 | P<0.01 | P<0.01 | P > 0.05 | P<0.001 | P<0.001 |

*FIGURE 10*